

# Exhibit 2

# FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)

*Get updates on the recalls*

## Update: 11/13/2019 - FDA warns Mylan for CGMP deviations

**Update [11/13/2019]** Today, the U.S. Food and Drug Administration posted a [warning letter](#) ([/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/mylan-laboratories-limited-unit-8-589297-11052019](#)) to Mylan Pharmaceuticals, Inc. in Chodavaram Village, Vizianagaram, Andhra Pradesh, India. Mylan manufactures valsartan active pharmaceutical ingredient (API) and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several current good manufacturing practice (CGMP) deviations at this Mylan facility, including failure to have adequate written procedures for the receipt, identification and handling of raw materials and failure to adequately clean equipment and utensils. Failure to correct these deviations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

## Update: 10/15/2019 - FDA warns Torrent for CGMP violations

**Update [10/15/2019]** Today, the U.S. Food and Drug Administration posted a [warning letter](#) ([/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/torrent-pharmaceuticals-limited-585255-10082019](#)) to Torrent Pharmaceuticals in Ahmedabad, Gujarat, India. Torrent manufactures losartan potassium tablets and has been one subject of an ongoing global investigation into nitrosamine impurities in angiotensin II receptor blockers (ARBs) such as valsartan, losartan and irbesartan.

The warning letter outlines several manufacturing violations at Torrent's Taluka-Kadi, Indrad, Gujarat facility, including failure to follow written procedures for production and process control and failure to adequately investigate batch discrepancies. Failure to correct

these violations may result in further action by the agency. The warning letter is another result of the agency's ongoing investigation.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

#### **Update: 9/20/2019 - Torrent expands its voluntary recall of losartan**

**Update [9/20/2019]** Torrent Pharmaceuticals is expanding its voluntary recall ([/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-o](#)) to include five additional lots of losartan potassium tablets (three lots of losartan potassium tablets and two lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited. Torrent is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\)](#) ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and](#)) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

#### **8/28/2019: STATEMENT: Statement on the agency's ongoing efforts to resolve safety issue with ARB medications**

Go to [FDA Statement](#) ([/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications](#))

#### **6/26/2019: UPDATE - Macleods Pharmaceuticals voluntarily recalls losartan containing NMBA**

**Update [6/26/2019]** FDA is alerting patients and health care professionals to Macleods Pharmaceuticals' voluntary [recall](#) ([/safety/recalls-market-withdrawals-safety-alerts/macleods-pharmaceutical-limited-issues-voluntary-nationwide-consumer-level-recall-losartan-potassium](#)) of two lots of losartan potassium tablets (50mg strength) and 30 lots of losartan potassium/hydrochlorothiazide (HCTZ) combination tablets (12 lots of

50mg/12.5mg strength, three lots of 100mg/12.5mg strength, and 15 lots of 100mg/25mg strength). This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs). The agency also updated the list of [recalled angiotensin II receptor blockers \(ARBs\)](#) ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valszartan-losartan-and](#)) .

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

#### **6/12/2019: UPDATE - Teva expands its voluntary recall of losartan**

**Update [6/12/2019]** Teva Pharmaceuticals is expanding its voluntary [recall](#) ([/safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-expands-voluntary-nationwide-recall-losartan-potassium-50-mg-and-100-mg](#)) to include seven additional lots of losartan potassium tablets (three lots of 50 mg strength and four lots of 100 mg strength) labeled by Golden State Medical Supply. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

The agency updated the list of [recalled angiotensin II receptor blockers \(ARBs\)](#) ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valszartan-losartan-and](#)) accordingly.

FDA reminds patients taking recalled ARBs to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

#### **5/6/2019: UPDATE - FDA alerts patients and health care professionals to Vivimed's recall of losartan medication due to NMBA**

**Update [5/6/2019]** FDA is alerting patients and health care professionals to a voluntary [recall](#) ([/safety/recalls-market-withdrawals-safety-alerts/vivimed-life-sciences-pvt-ltd-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-50-mg-and](#)) of 19 lots of

losartan potassium tablets made by Vivimed Life Sciences Pvt Ltd in Alathur, Chennai, India and distributed by Heritage Pharmaceuticals Inc, East Brunswick, New Jersey, due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). Vivimed is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit (<https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan#interimlimits2>) of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

The agency also updated the list of recalled ARBs (</drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and>).

## **5/2/2019: UPDATE - Laboratory analysis of valsartan products**

**Update [5/2/2019]** FDA posted laboratory test results showing NDEA levels in recalled valsartan products (</drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products>) as well as an assessment of the cancer risk from NDEA in valsartan.

## **4/29/2019: UPDATE - FDA alerts patients and health care professionals to Teva's recall and Legacy's expanded recall of losartan medication due to NMBA**

**Update [4/29/2019]** FDA is alerting patients and health care professionals to a voluntary recall (</safety/recalls-market-withdrawals-safety-alerts/teva-pharmaceuticals-usa-inc-issues-voluntary-nationwide-recall-losartan-potassium-25-mg-and-100-mg>) of 44 lots of losartan potassium tablets manufactured by Teva Pharmaceuticals and labeled as Golden State Medical Supply due to the detection of the impurity N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). The recalled products were made with active pharmaceutical ingredient (API) manufactured by Hetero Labs. Teva is recalling lots of losartan-containing medication that tested positive for NMBA above 9.82 parts per million.

Additionally, Legacy expanded its recall (</safety/recalls-market-withdrawals-safety-alerts/legacy-pharmaceutical-packaging-llc-expands-voluntary-nationwide-recall-losartan-potassium-tablets>) to include one additional lot of losartan tablets made with API

manufactured by Hetero Labs.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

The agency also updated the list of [recalled losartan medicines](#) ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and](#)).

#### **4/19/2019: UPDATE - Torrent further expands its voluntary recall of losartan; FDA posts new nitrosamine testing methods**

**Update [4/19/2019]** Torrent Pharmaceuticals Limited is further expanding its voluntary recall ([/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium](#)) to include 104 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

The agency updated the list of [losartan products under recall](#) ([/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and](#)) accordingly.

FDA reminds patients taking recalled angiotensin II receptor blockers (ARBs) to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition.

FDA is also posting new testing methods which can help manufacturers and international regulators detect and identify multiple nitrosamine impurities. FDA and international regulators have identified N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA) and NMBA in ARBs.

- A [direct injection GC-MS method](#) ([/media/123409/download](#)) that is able to detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- A [headspace GC-MS method](#) ([/media/124025/download](#)) that is able to detect NDMA, NDEA, NDIPA, and NEIPA

These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

**4/4/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the agency's list of known nitrosamine-free valsartan and ARB class medicines, as part of agency's ongoing efforts to resolve ongoing safety issue**

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-agencys-list-known-nitrosamine-free-valsartan-and-arb-class-medicines-part-agencys\)](#).

**3/22/2019: UPDATE - FDA updates recalled valsartan-containing and losartan-containing medicine information**

**Update [3/22/2019]** FDA has updated the [list of valsartan medicines under recall \(/media/118231/download\)](#) to incorporate additional repackagers of Aurobindo's valsartan-containing medicine. FDA has also updated the [list of losartan medicines under recall \(/media/119422/download\)](#) to include repackagers of Torrent's and Camber's losartan-containing medicines.

The agency also updated the [list of valsartan medicines not under recall \(/media/118232/download\)](#) accordingly.

**3/20/2019: UPDATE - FDA not objecting to losartan with NMBA below 9.82 ppm remaining on the market**

**Update [3/20/2019]** To ensure patient access to losartan, FDA will not object to certain manufacturers temporarily distributing losartan containing N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) above the [interim acceptable intake limit](#) of 0.96 parts per million (ppm) and below 9.82 ppm until the impurity can be eliminated. The agency expects many companies will be able to manufacture losartan without nitrosamine impurities and replenish the U.S. supply in approximately six months.

Agency scientists evaluated the risk of exposure to NMBA at levels up to 9.82 ppm and determined that it presents no meaningful difference in cancer risk over a six-month time period when compared to a lifetime of exposure to NMBA at 0.96 ppm. Distributing losartan containing NMBA up to 9.82 ppm, will help maintain adequate losartan supply while companies obtain approval for manufacturing processes that produce nitrosamine-free losartan for patients.

FDA reminds patients taking recalled losartan to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death. Untreated diabetic nephropathy (kidney disease) leads to worsening renal (kidney) disease.

Manufacturers should contact FDA's Drug Shortages Staff when their testing of losartan shows levels of NMBA that exceed the interim acceptable intake limit of 0.96 ppm. FDA will determine, on a case-by-case basis, whether lots containing NMBA greater than 0.96 ppm should be released for distribution.

FDA continues to work with companies and international regulators to ensure products entering the U.S. market do not contain nitrosamine impurities.

### **3/1/2019: UPDATE - Torrent again expands its voluntary recall of losartan; Hetero also voluntarily recalls losartan**

**Update [3/1/2019]** Torrent Pharmaceuticals Limited is further expanding its [voluntary recall](#) ([Updated: Torrent Pharmaceuticals Limited Issues Voluntary Nationwide Recall of Losartan Potassium Tablets, USP and Losartan Potassium /Hydrochlorothiazide Tablets, USP](#)) ↗ (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) to include 114 additional lots of losartan potassium and losartan potassium/hydrochlorothiazide combination tablets. This recall is due to unacceptable amounts of N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Today, the agency also issued a [press release](#) ([FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall](#)) to provide additional information about its ongoing investigation and another voluntary recall by Hetero/Camber Pharmaceuticals, which was announced on February 28, of 87 lots of losartan potassium tablets (25 mg, 50 mg and 100 mg). The recalled losartan potassium and losartan potassium/hydrochlorothiazide tablets are also manufactured by Hetero, which are distributed by Camber, and contain the impurity NMBA.

Torrent and Hetero/Camber are only recalling lots of losartan-containing medication with NMBA above the [interim acceptable intake limits](#) of 0.96 parts per million (ppm).

The agency also updated the list of [losartan products under recall](#) (</media/119422/download>).

### **3/1/2019: UPDATE - Aurobindo expands its voluntary recall of valsartan and amlodipine/valsartan**

**Update [3/1/2019]** AurobindoPharma USA is expanding its voluntary recall (AurobindoPharma USA, Inc. Initiates a Voluntary Nationwide Consumer Level Recall Expansion of 38 Lots of Amlodipine Valsartan Tablets USP and Valsartan Tablets, USP due to the detection of NDEA (N-Nitrosodiethylamine) Impurity.) to include 38 additional lots of valsartan and amlodipine/valsartan combination tablets. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine.

Aurobindo is only recalling lots of valsartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.083 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the valsartan products under recall (</media/118231/download>).

### **3/1/2019: PRESS RELEASE - FDA provides update on its ongoing investigation into ARB drug products; reports on finding of a new nitrosamine impurity in certain lots of losartan and product recall**

Go to Press Release (<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632425.htm>)

### **FDA updates table of interim limits for nitrosamine impurities in ARBs**

**Update [2/28/2019]** FDA is posting the updated table of interim acceptable intake limits for nitrosamine impurities to reflect N-Nitroso-N-methyl-4-aminobutyric acid (NMBA) limits, which are the same as those for NDMA.

The agency will use the interim limits below to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

Not all ARB products contain NDMA, NDEA or NMBA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

## Interim Limits for NDMA, NDEA, and NMBA in Angiotensin II Receptor Blockers (ARBs)

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
<b>Valsartan</b>	320	96	0.3	26.5	0.083	96	0.3
<b>Losartan</b>	100	96	0.96	26.5	0.27	96	0.96***
<b>Irbesartan</b>	300	96	0.32	26.5	0.088	96	0.32
<b>Azilsartan</b>	80	96	1.2	26.5	0.33	96	1.2
<b>Olmesartan</b>	40	96	2.4	26.5	0.66	96	2.4
<b>Eprosartan</b>	800	96	0.12	26.5	0.033	96	0.12
<b>Candesartan</b>	32	96	3.0	26.5	0.83	96	3.0
<b>Telmisartan</b>	80	96	1.2	26.5	0.33	96	1.2

\* The acceptable intake is a daily exposure to a compound such as NDMA, NDEA, or NMBA that approximates a 1:100,000 cancer risk after 70 years exposure

\*\* These values are based on a drug's maximum daily dose as reflected in the drug label

\*\*\* FDA is temporarily not objecting to losartan with NMBA below 9.82 ppm remaining on the market

### 2/25/2019: UPDATE - Losartan distributed by Macleods Pharmaceuticals voluntarily recalled

**Update [2/25/2019]** FDA is alerting patients and health care professionals to a voluntary recall of one lot of losartan potassium/hydrochlorothiazide (HCTZ) 100mg/25mg combination tablets manufactured by Macleods Pharmaceuticals. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) found in the medicine made with active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Macleods is only recalling lots of losartan-containing medication where NDEA has been detected above the interim acceptable intake limit of 0.27 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin II receptor blockers (ARBs).

The agency also updated the list of losartan products under recall ([/media/119422/download](#)).

**1/25/2019: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues**

Go to [FDA Statement \(/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-and-arb-class-impurities-and-agencys-steps\)](#)

**1/23/2019: UPDATE - Torrent further expands its voluntary recall of losartan**

**Update [1/23/2019]** Torrent Pharmaceuticals is further expanding its [voluntary recall \(/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium\)](#) to include six additional lots of losartan potassium and hydrochlorothiazide combination tablets, for a total of 16 lots of losartan-containing medicines. This recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan-containing medication containing NDEA above the [interim acceptable intake limits](#) of 0.27 parts per million (ppm).

The agency also updated the list of [losartan medications under recall \(/media/119422/download\)](#).

**1/18/2019: UPDATE - Irbesartan distributed by Solco Healthcare voluntarily recalled**

**Update [1/18/2019]** FDA is alerting patients and health care professionals to a voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/prinston-pharmaceutical-inc-issues-voluntary-nationwide-recall-irbesartan-and-irbesartan-hctz\)](#) of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Prinston Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of N-Nitrosodiethylamine (NDEA) in the irbesartan active pharmaceutical ingredient manufactured by Zhejiang Huahai Pharmaceuticals (ZHP).

Solco is only recalling lots of irbesartan-containing medication where NDEA has been detected above the [interim limit](#) of 0.088 parts per million. FDA is working with manufacturers to reduce and remove nitrosamines from angiotensin receptor II blockers (ARBs).

The agency also updated the list of irbesartan products under recall.

### 1/3/2019: UPDATE - Torrent expands its voluntary recall of losartan

**Update [1/3/2019]** Torrent Pharmaceuticals is expanding its voluntary recall ([/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-expands-voluntary-nationwide-recall-losartan-potassium-tablets-usp](#)) to include eight additional lots of losartan potassium tablets, for a total of 10 lots. This recall is due to trace amounts of N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Torrent is only recalling lots of losartan medication containing NDEA above the interim acceptable intake level of 0.27 parts per million.

The agency also updated the list of list of valsartan products under recall ([/media/118231/download](#)).

### 1/2/2019: UPDATE - FDA alerts patients and health care professionals to Aurobindo's recall of valsartan medication due to NDEA

**Update [1/2/2019]** FDA is alerting patients and health care professionals to Aurobindo Pharma USA's voluntary recall ([/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-usa-inc-initiates-voluntary-nationwide-consumer-level-recall-80-lotsamlodipine](#)) of two lots of valsartan tablets, 26 lots of amlodipine and valsartan combination tablets, and 52 lots of valsartan and hydrochlorothiazide (HCTZ) combination tablets due to the amount of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient. Aurobindo is recalling amlodipine and HCTZ only in combination medications containing valsartan. Neither amlodipine nor HCTZ is currently under recall by itself.

Aurobindo is recalling lots of valsartan-containing medication that tested positive for NDEA above the interim acceptable daily intake level of 0.083 parts per million.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above interim acceptable daily intake levels.

FDA also updated the list of valsartan products under recall ([/media/118231/download](#)) and the list of valsartan products not under recall ([/media/118232/download](#)).

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor prescribes a different medication that treats the same condition. Some ARBs contain no NDMA or NDEA.

### **12/20/2019: UPDATE - FDA alerts patients and health care professionals to Torrent's recall of losartan medication due to NDEA**

**Update [12/20/2018]** FDA is alerting patients and health care professionals to Torrent Pharmaceuticals' voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/updated-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-losartan-potassium\)](#) of two lots of losartan potassium 100 mg tablets due to N-Nitrosodiethylamine (NDEA) in the losartan active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited.

Not all Torrent losartan-containing medications distributed in the U.S. are being recalled. Torrent is recalling only those lots of losartan medication that tested positive for NDEA above the acceptable daily intake of 0.27 ppm.

The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable daily intake levels.

FDA posted a list of [losartan medications under recall \(/media/119422/download\)](#). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

### **12/19/2018: UPDATE - FDA presents interim limits of nitrosamines in currently marketed ARBs**

**Update [12/19/2018]** FDA is publishing interim acceptable intake levels of nitrosamine impurities in angiotensin II receptor blockers (ARBs) for manufacturers to use to ensure their finished drug products are safe for patients.

The agency evaluated safety data for N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) to determine an interim acceptable intake level for these impurities in the ARB class. NDMA and NDEA are probable human carcinogens and should

not be present in drug products. We are currently aware of NDMA and NDEA in certain valsartan, irbesartan and losartan-containing products, and those products and some active pharmaceutical ingredients (API) used to manufacture them have been recalled from the U.S. market. See the [list of valsartan products under recall \(/media/118231/download\)](#) and the [list of irbesartan products under recall \(/media/118233/download\)](#).

Drug products that contain NDMA or NDEA above the limits in the table below pose an unacceptable risk to patients. The agency will use the interim limits to recommend manufacturers conduct a voluntary recall if laboratory testing confirms the presence of nitrosamine impurities in finished drug product. FDA is working with industry and international regulators to ensure products entering the market do not contain these impurities, but we are tolerating the impurities below the level established in the table for a short period of time to avoid a possible shortage of ARBs.

The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects a new impurity or higher level of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients. To aid industry and regulatory agencies, FDA has developed and published methods to detect NDMA and NDEA impurities – the gas chromatography/mass spectrometry (GC/MS) headspace method ([/media/115965/download](#)), the [combined GC/MS headspace method \(/media/117843/download\)](#), and the [combined GC/MS direct injection method \(/media/117807/download\)](#). These methods can be used for drug substances and products, and users should validate them as part of good manufacturing practices and where data are used to support a regulatory submission or required quality assessment of the API or drug product.

Not all ARB products contain NDMA or NDEA impurities, so pharmacists may be able to provide an alternative medication not affected by the recalls, or health care professionals may prescribe a different medication that treats the same condition.

### **Interim Limits for NDMA and NDEA in Angiotensin II Receptor Blockers (ARBs)**

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**
<b>Valsartan</b>	320	96	0.3	26.5	0.083
<b>Losartan</b>	100	96	0.96	26.5	0.27
<b>Irbesartan</b>	300	96	0.32	26.5	0.088

Azilsartan	80	96	1.2	26.5	0.33
Olmesartan	40	96	2.4	26.5	0.66
Eprosartan	800	96	0.12	26.5	0.033
Candesartan	32	96	3.0	26.5	0.83
Telmisartan	80	96	1.2	26.5	0.33

\* The acceptable intake is a daily exposure to a compound such as NDMA or NDEA that results in a 1:100,000 cancer risk after 70 years exposure

\*\* These values are based on a drug's maximum daily dose as reflected in the drug label

For comparison with the levels of NDMA found in some common foods, please see our Aug. 20, 2018, update.

#### **12/12/2018: UPDATE - FDA updates NDMA and NDEA detection methods, announces posting of ZHP warning letter**

**Update [12/12/2018]** The FDA has updated its testing methods to detect NDMA and NDEA impurities – the ([\(!--\\$ssDownloadLink\('UCM618053'\)--\]\)GC/MS](#)) headspace method ([/media/115965/download](#)), the combined headspace method ([/media/117843/download](#)), and the combined direct injection method ([/media/117807/download](#)) – by adding the limits of detection (LOD) and clarifying that the methods can be used for both drug substances and drug products. These methods were validated with respect to valsartan drug substances and drug products, but the agency expects them to have comparable LODs and limits of quantitation (LOQ) for other angiotensin II receptor blockers (ARB).

The agency also issued a press release announcing the posting of a warning letter the agency issued Nov. 29 to Zhejiang Huahai Pharmaceuticals Co. Ltd. (ZHP).

#### **12/11/2018: PRESS RELEASE - FDA warns API manufacturer involved in valsartan recall, provides information for patients taking these medications**

Go to [Press Release \(/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these\)](#)

#### **12/6/2018: UPDATE - Mylan expands its voluntary recall of valsartan-containing products**

**Update [12/6/2018]** Mylan Pharmaceuticals is expanding its voluntary recall ([!-\$wcmUrl('link','UCM627647')--]) to include all lots of non-expired valsartan-containing products due to trace amounts of N-Nitrosodiethylamine (NDEA) in the valsartan active pharmaceutical ingredient (API) manufactured by Mylan Laboratories Limited. The 104 additional lots include 26 lots of amlodipine and valsartan tablets, 51 lots of valsartan tablets and 27 lots of valsartan and hydrochlorothiazide tablets. These lots were distributed in the U.S. between March 2017 and November 2018.

The agency also updated the [list of valsartan products under recall \(/media/118231/download\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#).

#### **11/27/2018: UPDATE - FDA alerts patients and health care professionals to Teva's recall of valsartan products due to NDEA**

**Update [11/27/2018]** FDA is alerting patients and health care professionals to Teva Pharmaceuticals' voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts\)](#) of valsartan-containing products manufactured using active pharmaceutical ingredient (API) from Mylan Pharmaceuticals. Mylan voluntarily [recalled \(/safety/recalls-market-withdrawals-safety-alerts\)](#) valsartan-containing products on November 20.

Teva is recalling all lots of amlodipine and valsartan combination tablets and amlodipine, valsartan, and hydrochlorothiazide (HCTZ) combination tablets due to the presence of N-Nitrosodiethylamine (NDEA). Teva has recalled other valsartan-containing products in recent months due to the presence of N-Nitrosodimethylamine (NDMA). With this recall, Teva has now recalled all their unexpired valsartan-containing products from the U.S. market.

The agency continues to investigate and test all angiotensin II receptor blocker (ARBs) for the presence of NDMA and NDEA and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated the [list of valsartan products under recall \(/media/118231/download\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#). The agency reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know that not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

## **11/21/2018: UPDATE - FDA alerts patients and health care professionals to Mylan's recall of valsartan products due to NDEA**

**Update [11/21/2018]** FDA is alerting patients and health care professionals to Mylan Pharmaceuticals' voluntary recall of 15 lots of valsartan-containing products due to the presence of N-Nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the U.S. are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and N-Nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of [valsartan products under recall \(/media/118231/download\)](#) and [valsartan products not under recall \(/media/118232/download\)](#). Additionally, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

## **11/9/2018: UPDATE - FDA alerts patients and health care professionals to Sandoz's losartan potassium and hydrochlorothiazide recall of one lot due to NDEA**

**Update [11/9/2018]** FDA is alerting patients and health care professionals to Sandoz's voluntary [recall \(/safety/recalls-market-withdrawals-safety-alerts/sandoz-inc-issues-voluntary-nationwide-recall-one-lot-losartan-potassium-and-hydrochlorothiazide-due\)](#) of one lot – JB8912 – of losartan potassium and hydrochlorothiazide 100mg/25mg tablets, that contain losartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide, a diuretic, used in combination for the treatment of hypertension. Sandoz's product was made using an active pharmaceutical ingredient (API) that has tested positive for NDEA. The API was manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd, which is on [import alert \(\[https://www.accessdata.fda.gov/cms\\\_ia/importalert\\\_189.html\]\(https://www.accessdata.fda.gov/cms\_ia/importalert\_189.html\)\)](#).

Sandoz's losartan drug products make up less than 1 percent of the total losartan drug products in the U.S. market.

FDA continues to investigate the presence of NDEA and NDMA, which are probable human carcinogens, in ARBs and is taking swift action when it identifies unacceptable impurities in API and finished drug products.

FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDEA or NDMA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

#### **10/30/2018: UPDATE - FDA alerts patients and health care professionals to ScieGen's irbesartan recall due to NDEA**

*Certain irbesartan products labeled as Westminster Pharmaceuticals Inc. and GSMS Inc. recalled*

**Update [10/30/2018]** FDA is alerting patients and health care professionals to ScieGen's voluntary recall of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain N-Nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen (causes cancer). FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply, Inc. (GSMS). See the [list of irbesartan products under recall \(/media/117814/download\)](#). This is the first non-valsartan drug product the agency has found to contain the NDEA impurity.

ScieGen's recall affects about 1 percent of the irbesartan drug products in the U.S. market.

Additionally, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/aurobindo-pharma-limited-issues-voluntary-recall-irbesartan-drug-substance-due-detection-trace\)](#) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of their irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or N-Nitrosodimethylamine (NDMA), a probable human carcinogen previously found in certain recalled valsartan products, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA. FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The [combined headspace](#)

method ([/media/117843/download](#)) and the combined direct injection method ([/media/117807/download](#)) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers to ensure their products are not at risk for NDMA or NDEA formation. The agency reminds manufacturers they are responsible for developing and using suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

For additional information about ARB products, see:

- list of valsartan products under recall ([/media/118231/download](#))
- list of valsartan products not under recall ([/media/118232/download](#))

#### **10/24/2018: UPDATE - FDA updates recalled valsartan-containing product information**

**Update [10/24/2018]** FDA continues to evaluate valsartan-containing products and other angiotensin II receptor blockers (ARBs), and has updated the list of products included in the recall ([/media/118231/download](#)) to add one additional lot of RemedyRepack.

#### **10/16/2018: UPDATE - FDA releases additional NDMA/NDEA detection method**

**Update [10/16/2018]** FDA is posting a gas chromatography-tandem mass spectrometry (GC-MS/MS) method ([/media/117807/download](#)) utilizing liquid injection for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

This method provides an additional option for regulators and industry to detect NDMA and NDEA impurities. This method can be used alone or in combination with the combined gas chromatography-mass spectrometry (GC/MS) headspace method ([/media/117843/download](#)) the agency recently posted. Like the previously posted methods, this method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

## **10/11/2018: UPDATE - FDA releases method for detection and quantification of both NDMA and NDEA**

**Update [10/11/2018]** ] FDA is posting a redeveloped combined gas chromatography-mass spectrometry (GC/MS) headspace ([/media/117843/download](#)) method for detecting the presence of impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) in valsartan drug products.

FDA previously posted a GC/MS method for detection of NDMA in valsartan products. Upon detection of NDEA in valsartan products manufactured by Zhejiang Huahai Pharmaceuticals, FDA redeveloped the testing method so that it can be used to detect and quantify levels of both NDMA and NDEA. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

FDA is also working on a GC/MS direct injection method for detection of NDMA and NDEA. We will post the method when it is available. This will provide an additional option for regulators and industry to use to detect both impurities.

## **10/5/2018: UPDATE - FDA posts laboratory analysis of NDMA levels in recalled valsartan products**

**Update [10/5/2018]** FDA posted laboratory test results showing NDMA levels in recalled valsartan products. FDA will also post test results ([/drugs/drug-safety-and-availability/laboratory-analysis-valsartan-products](#)) and an assessment of the cancer risk from NDEA when they are available.

## **9/28/2018: UPDATE - FDA places Zhejiang Huahai Pharmaceuticals on import alert**

**Update [9/28/2018]** FDA placed Zhejiang Huahai Pharmaceuticals on import alert ([https://www.accessdata.fda.gov/cms\\_ia/importalert\\_189.html](https://www.accessdata.fda.gov/cms_ia/importalert_189.html)) on September 28, 2018, to protect U.S. patients while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent inspection ([/media/117875/download](#)) at ZHP's facility.

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or higher levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.

#### **9/24/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan**

**Update [9/24/2018]** FDA has updated the [list of valsartan products not under recall](#) ([/media/118232/download](#)) with five Teva products that were not previously on either list.

#### **9/13/2018: PRESS RELEASE - FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products**

Go to [Press Release](#) ([/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional](#)).

#### **8/30/2018: STATEMENT - Statement from FDA Commissioner Scott Gottlieb, M.D., and Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings**

Go to [FDA Statement](#) ([/news-events/press-announcements/fda-statement-fdas-ongoing-investigation-valsartan-impurities-and-recalls-and-update-fdas-current](#)).

#### **8/24/2018: UPDATE - FDA updates recall lists**

**Update [8/24/2018]** Torrent Pharmaceuticals Limited is expanding its voluntary [recall](#) ([/safety/recalls-market-withdrawals-safety-alerts/updatedadditional-lots-added-torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall](#)). FDA has updated the [list of valsartan products under recall](#) ([/media/118231/download](#)).

#### **8/22/2018: UPDATE - FDA updates recall lists and releases method for the detection and quantification of NDMA in valsartan**

**Update [8/22/2018]** Torrent Pharmaceuticals Limited is expanding its voluntary recall to all lots of unexpired valsartan-containing drug products due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai

Pharmaceuticals.

RemedyRepack, a repackager of Torrent's valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets, has also recalled.

FDA has updated the [list of valsartan products under recall \(/media/118231\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#).

Additionally, FDA is releasing a gas chromatography-mass spectrometry (GC/MS) [headspace method \(/media/115965/download\)](#) for manufacturers and regulators to detect and quantify NDMA in valsartan API and finished drug products. The agency is using this method to test potential NDMA-containing APIs and drug products. This method should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.

#### **8/20/2018: UPDATE - FDA updates recalled valsartan-containing product information and presents NDMA levels in some foods**

**Update [8/20/2018]** FDA is alerting health care professionals and patients that Torrent Pharmaceuticals Limited is voluntarily [recalling \(/safety/recalls-market-withdrawals-safety-alerts/torrent-pharmaceuticals-limited-issues-voluntary-nationwide-recall-valsartan-amlodipine-hctz-tablets\)](#) 14 lots of valsartan/amlodipine/hydrochlorothiazide (HCTZ) tablets. Not all Torrent valsartan products distributed in the U.S. are being recalled.

FDA recently learned Torrent used affected valsartan active pharmaceutical ingredient (API) manufactured by Zhejiang Huahai Pharmaceuticals. FDA testing confirmed NDMA in some Torrent products.

To date, Torrent has not received any reports of adverse events related to this recall.

FDA has updated the [list of valsartan products under recall \(/media/118231\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#) to incorporate additional repackagers of Camber's valsartan products and Torrent's recall.

NDMA is a known environmental contaminant. For context, it is found in water and foods including meats, dairy products and vegetables.

#### **Estimated Range of Daily NDMA Consumption for certain foods (Recommended daily food consumption rates based on [Dietary Guidelines for Americans 2015-2020](#) (<https://health.gov/dietaryguidelines/2015/guidelines/>))**

- Cured meat - 0.004-0.23 micrograms<sup>1</sup>

- Smoked meat - 0.004-1.02 micrograms<sup>1</sup>
- Grilled meat - 0.006-0.13 micrograms<sup>1</sup>
- Bacon - 0.07-0.09 micrograms<sup>2</sup>
  - In more ordinary terms, for example, one pound of bacon may contain 0.304-0.354 micrograms of NDMA

FDA reminds patients taking valsartan from a recalled lot that they should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. Not all valsartan products contain NDMA, so pharmacists may be able to provide a refill of valsartan medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

<sup>1</sup> Mavelle, T., B. Bouchikhi, and G. Debry, *The occurrence of volatile N-nitrosamines in French foodstuffs. Food Chemistry*, 1991. 42(3): p. 321-338.

<sup>2</sup> Park, J., et al., *Distribution of Seven N-Nitrosamines in Food. Toxicol Res*, 2015. 31(3): p. 279-288.

## 8/9/2018: UPDATE - FDA updates recalled valsartan-containing product information

**Update [8/9/2018]** FDA has updated the [list of valsartan products under recall \(/media/118231\)](#) and the [list of valsartan products not under recall \(/media/118232/download\)](#) to incorporate recalls of valsartan-containing products manufactured by Hetero Labs Limited, in India, labeled as Camber Pharmaceuticals Inc. Not all Camber valsartan products distributed in the U.S. are being recalled.

Camber Pharmaceuticals is [recalling \(/safety/recalls-market-withdrawals-safety-alerts/camber-pharmaceuticals-inc-issues-voluntary-nationwide-recall-valsartan-tablets-usp-40mg-80mg-160mg\)](#) certain valsartan tablets because they contain the impurity N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient (API). Hetero Labs manufactures the API for the Camber products using a process similar to Zhejiang Huahai Pharmaceuticals.

Test results from Hetero Labs show the amount of NDMA found in its valsartan API exceeds acceptable levels; although it is generally lower than the amount discovered in the API manufactured by Zhejiang.

FDA is testing samples of valsartan API and finished products to confirm the extent and amount of NDMA and help inform the ongoing investigation. The agency has also contacted other manufacturers of valsartan API to determine if their manufacturing processes are at risk for the formation of NDMA, and is working with them to ensure NDMA is not present in future valsartan API.

Valsartan is an angiotensin II receptor blocker (ARB), and FDA is investigating whether other types of ARBs are at risk for the presence of NDMA.

Recalled valsartan products labeled as Camber may be repackaged by other companies. FDA will provide updates as more information becomes available.

#### **8/2/2018: UPDATE - FDA updates recalled valsartan-containing product information and reminds API manufacturers to evaluate processes for unsafe impurities**

**Update [8/2/2018]** FDA continues to evaluate valsartan-containing products and has updated the [list of products included in the recall \(/media/118231/download\)](#) and the [list of products not included in the recall \(/media/118232/download\)](#). In addition to updating the lists, FDA revised information related to A-S Medication on the list of products included in the recall. The agency will continue to provide information when it becomes available.

FDA is working with drug manufacturers to ensure future valsartan active pharmaceutical ingredients (APIs) are not at risk of NDMA formation. The agency reminds manufacturers to thoroughly evaluate their API manufacturing processes, and changes to those processes, to detect any unsafe impurities. If a manufacturer detects new or higher levels of impurity, they should take action to prevent changes to the product's safety profile.

#### **7/27/2018: UPDATE - FDA updates recalled valsartan-containing product information**

**Update [7/27/2018]** FDA is updating health care professionals and patients after discovering that several additional companies that repackage drug products are also recalling valsartan-containing products.

FDA has product recall information from three additional repackagers of valsartan-containing products made by Teva Pharmaceuticals and Prinston Pharmaceuticals Inc. – labeled as A-S Medication Solutions LLC, AvKARE and RemedyRepack – and the agency has added them to the recalled products list. Two of these companies, A-S Medication and RemedyRepack, may also distribute valsartan products not affected by the recall. The agency is confirming this information and will provide an update once it is available.

The following additional repackagers are recalling or are expected to recall valsartan-containing products. FDA is working to gather product recall information from these companies and has removed them from the list of products that are not impacted by this recall:

- Bryant Ranch Prepack Inc.
- H. J. Harkins Company Inc. (*this company was not originally included on either list*)
- Lake Erie Medical, doing business as Quality Care Products LLC
- NuCare Pharmaceuticals Inc.
- Northwind Pharmaceuticals
- Proficient Rx

It is possible that not all valsartan-containing products repackaged by these companies are impacted by the recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](#) and the [list of products not included in the recall \(/media/118232/download\)](#) as more information becomes available.

#### **7/27/2018: UPDATE - Analysis of N-nitrosodimethylamine (NDMA) Levels in Recalled Valsartan in the U.S.**

**Update [7/27/2018]** On July 13th, FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA). Valsartan is a medication commonly used to treat high blood pressure and heart failure.

NDMA has been found to increase the occurrence of cancer in animal studies. These animal studies were done using amounts of NDMA much higher than the impurity levels in recalled valsartan batches. Based on these animal studies, the U.S. Environmental Protection Agency considers [NDMA a probable human carcinogen](#) ([https://www.epa.gov/sites/production/files/2017-10/documents/ndma\\_fact\\_sheet\\_update\\_9-15-17\\_508.pdf](https://www.epa.gov/sites/production/files/2017-10/documents/ndma_fact_sheet_update_9-15-17_508.pdf))—a chemical that can increase the risk of cancer in humans. NDMA is found in some water supplies and in some foods<sup>1</sup>. Consuming up to 96 nanograms NDMA/day is considered reasonably safe for human ingestion<sup>2</sup>. It is estimated that over the course of a person's lifetime, consuming this amount of NDMA would result in less than one additional case of cancer for every 100,000 people. To put this in context, currently one out of every three people in the US will experience cancer in their lifetime.

The amounts of NDMA found in the recalled batches of valsartan exceeded these acceptable levels. The agency wanted to put some context around the actual potential risk posed to patients who used versions of valsartan that may have contained high levels of NDMA. Based on records from the manufacturer of the recalled valsartan, some levels of the impurity may have been in the valsartan-containing products for as long as four years. FDA scientists estimate that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people. This assessment led to FDA's decision to have these batches recalled.

Patients taking valsartan from a recalled batch should continue taking their current medicine until their doctor or pharmacist provides a replacement or a different treatment option. It is important to know that not all valsartan products contained NDMA, so pharmacists may be able to provide a refill of valsartan medication from batches that are not affected by the recall, or doctors may prescribe a different medication that treats the same indications.

**FDA continues to evaluate the safety of valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](#) and the [list of products not included in the recall \(/media/118232/download\)](#) as more information becomes available. If you are taking a valsartan product, be sure to check back as the lists may change.

<sup>1</sup> From Toxnet: <https://toxnet.nlm.nih.gov/> (<https://toxnet.nlm.nih.gov/>)

**Average Daily Intake:** WATER: (assume 3 to 6 ng N-nitrosodimethylamine/l)(1) 6 to 12 ng; direct intake from drinking water is probably much less than 1 ug/day(2). FOOD: (assume <0.1 to="" 84="" ug/kg)(4)=><0.16 to="" 134="" >

[<sup>1</sup>(1) Kimoto WI et al; Water Res 15: 1099-1106 (1981) (2) USEPA; Ambient Water Quality Criteria Doc: Nitrosamines p.C-14 (1980) EPA 440/5-80-064 (4) IARC; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 17: 125-76 (1978)]

<sup>2</sup> The calculated acceptable intake for NDMA is based on methods described in the ICH Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk ([http://wcmis-internet.fda.gov/files/drugs/published/M7\\_R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf](http://wcmis-internet.fda.gov/files/drugs/published/M7_R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf))

[Case 1:19-md-02875-RMB-SAK Document 1702-3 Filed 12/01/21 Page 27 of 31](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-) (http://wcms-internet.fda.gov/files/drugs/published/M7-R1-

PageID: 49418

[AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf](http://wcms-internet.fda.gov/files/drugs/published/M7-R1-AssessmentAndControlOfDNA-Reactive-Mutagenic-ImpuritiesInPharmaceuticalsToLimitPotentialCarcinogenicRisk-Guidance.pdf))

### **7/24/2018: UPDATE - FDA publishes a list of valsartan-containing products not part of the recall**

**Update [7/24/2018]** FDA is updating health care professionals and consumers on the agency's progress in responding to the ongoing recalls of valsartan, which is used to treat high blood pressure and heart failure, due to the presence of NDMA. The agency has posted a [list of valsartan-containing products not impacted \(/media/118232/download\)](#) by this recall. **FDA continues to evaluate valsartan-containing products** and will update the [list of products included in the recall \(/media/118231/download\)](#) and the [list of products not included in the recall \(/media/118232/download\)](#) as more information becomes available.

Manufacturers of these products often produce multiple dosage strengths, however not all of them are being recalled. FDA recommends health care professionals and patients carefully check these lists. Health care professionals and patients should check this statement frequently for any updates.

FDA reminds consumers to continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option. Untreated hypertension (high blood pressure) leads to an increase in the risk of heart attacks and stroke. Untreated heart failure increases the risk of hospitalization and death.

Consumers and health care professionals should continue to report any adverse reactions with valsartan-containing products, to the [FDA's MedWatch program \(/medwatch-fda-safety-information-and-adverse-event-reporting-program\)](#) to help the agency better understand the scope of the problem:

- Complete and submit the report online at [www.fda.gov/medwatch/report.htm](http://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>)
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178 

### **7/18/2018: STATEMENT - FDA updates health care professionals and patients on recent valsartan recalls**

**[7/18/2018]** The U.S. Food and Drug Administration is updating health care professionals and consumers following a recent [FDA press release](#) ([/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity](#)) about voluntary recalls of several drug products containing the active pharmaceutical ingredient (API) valsartan. Valsartan is used to treat high blood pressure and heart failure. Not all products containing valsartan are being recalled, and this update will clarify which valsartan-containing products are being recalled.

The recalled products contain an impurity, N-nitrosodimethylamine (NDMA), in the API manufactured by Zhejiang Huahai Pharmaceuticals, Linhai, China. The presence of the potentially cancer-causing NDMA was unexpected, and the agency believes the NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.

**The investigation into valsartan-containing products is ongoing, and the following list may change. We will update this statement as we have more information.**

There are currently three voluntary recalls related to the NDMA impurity detected in the valsartan API:

- **Teva Pharmaceuticals USA labeled as Major Pharmaceuticals** — recall is at the **retail level** because these products are only used in facilities where they are directly administered to patients by health care professionals: Valsartan 80 mg and 160 mg products;
- **Prinston Pharmaceuticals Inc. labeled as Solco Healthcare LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products; and
- **Teva Pharmaceuticals labeled as Actavis LLC** — recall is at the **consumer/user level**: Valsartan 40 mg, 80 mg, 160 mg, and 320 mg; and valsartan/HCTZ 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, and 320 mg/25 mg products.

[Detailed list of products included in the recall](#) ([/media/118231/download](#)) (PDF - 87 KB)

### **What should patients know:**

- Continue taking your current medicine until your doctor or pharmacist gives you a replacement or a different treatment option.
- Not all valsartan-containing medications are affected and being recalled.

- If you are taking any medication containing valsartan, compare the information on your prescription bottle with [the information in this list \(/about-fda/page-not-found\)](#) (company, National Drug Code, lot number) to determine if your current medicine has been recalled. If you are not certain, contact your pharmacist.
- If you have medicine included in the recall, contact your pharmacist. The pharmacist may be able to provide you with valsartan made by another company. If not, contact your doctor immediately to discuss other treatment options.

### **What health care professionals should know:**

- FDA has determined the recalled valsartan products pose an unnecessary risk to patients. Therefore, FDA recommends patients use valsartan-containing medicines made by other companies or consider other available treatment options for the patient's medical condition.
- If you have medication samples from these companies, quarantine the products and do not provide them to patients.

Consumers and health care professionals should report any adverse reactions with valsartan-containing products, to the FDA's [MedWatch program](#) (<https://www.fda.gov/safety/medwatch/>) to help the agency better understand the scope of the problem:

- Complete and submit the report online at [www.fda.gov/medwatch/report.htm](https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) (<https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>)
- Download and complete the appropriate form, then submit it via fax at 1-800-FDA-0178 

### **7/13/2018: PRESS RELEASE - FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity**

Go to [Press Release \(/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.\)](#)

### **FDA-published testing methods to provide options for regulators and industry to detect NDMA and NDEA impurities**

**The links below are to FDA-published testing methods to provide options for regulators and industry to detect nitrosamine impurities in ARB drug substances and drug products. These methods should be validated by the user if the resulting data are used to support a required quality assessment of the API or drug product, or if the results are used in a regulatory submission.**

- Combined headspace method (</media/117843/download>): a GC/MS method that allows determination of both N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously
- Combined direct injection method (</media/117807/download>): a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously
- Direct injection GC-MS method (</media/123409/download>): a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA)
- Headspace GC-MS method (</media/124025/download>): a method that can detect NDMA, NDEA, NDIPA, and NEIPA
- LC-HRMS method (</media/125478/download>): a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA)
- RapidFire-MS/MS method (</media/125477/download>): a method that can detect NEIPA, NDIPA, NDBA, and NMBA. We do not recommend using this method to detect NDMA or NDEA because it is less sensitive to those impurities.

The LC-HRMS and RapidFire-MS/MS methods are the first methods FDA has posted for detecting NMBA. The European Directorate for the Quality of Medicines (EDQM) has also published methods to detect NDMA and NDEA (<https://www.edqm.eu/en/ad-hoc-projects-omcl-network>) ↗ (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>). FDA has not validated EDQM's methods.

## Resources for You

- Search ARBs Recalls List (</drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valszartan-losartan-and>)
- Recalls of ARBs including Valsartan, Losartan and Irbesartan (</drugs/drug-safety-and-availability/recalls-angiotensin-ii-receptor-blockers-arbs-including-valszartan-losartan-and-irbesartan>)

- [Nitrosamine Impurities in Medications \(/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications\)](#)